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(57) Abstract

A method of treatment is provided to treat inflammation associated with human neutrophil elastase mediated disorders, particularly diseases of respiratory system or oral cavity. The method comprises a combined therapy of administering an elastase inhibitor(s) with an antibacterial agent(s), directed against pathogenic bacteria associated with disease of the respiratory system and oral cavity. A pharmaceutical composition comprising at least one antibacterial agent, and at least one elastase inhibitor is provided, preferably in aerosolized form, as well as a kit containing the respective components in separate packages.

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COMBINED THERAPY FOR TREATMENT OF INFLAMMATION USING ELASTASE INHIBITOR(S) AND ANTIBACTERIAL AGENT(S)

This application claims the benefit of U.S. Provisional Application No. 60/100,386, filed September 15, 1998.

FIELD OF THE INVENTION

The present invention relates to a method of using antibacterial agent(s), in combination with human neutrophil elastase inhibitor(s) for the treatment of inflammation, particularly inflammation associated with pulmonary disease and dental disease.

BACKGROUND OF THE INVENTION

Pulmonary inflammation has been associated with aberrant levels of or aberrant activity of human neutrophil elastase (HNE), a member of the family of serine proteases. HNE is known to degrade a variety of connective tissue proteins. HNE has been implicated in the pathogenesis of several chronic inflammatory diseases of the lung.

Under normal conditions, the proteolytic activity of HNE is controlled by several natural protease inhibitors. The primary guardian against connective tissue destruction is alpha-1 protease inhibitor (α_1-PI). Although α_1-PI associates with HLE very quickly and irreversibly, several pathological conditions may arise, for example, when α_1-PI levels are genetically low, or when α_1-PI has been oxidized or degraded, or when access to HNE is restricted. Disease states resulting from uncontrolled elastase activity include, for example, cystic fibrosis, rheumatoid arthritis, bronchitis, bronchiectasis, emphysema, adult respiratory distress syndrome, periodontitis and other related diseases. A number of synthetic HNE inhibitors have shown some effectiveness in treating inflammation resulting from uncontrolled elastase activity, particularly in the lung.

In the disease state of cystic fibrosis (CF), the level of elastase is very high in spite of the presence of its natural inhibitor (α_1 -PI) in higher concentration. It is reported that majority of α_1-PI in CF lungs is present in an inactive form and thus there is an imbalance between elastase and its natural inhibitor, α_1-PI.

Many potent elastase inhibitors have been synthesized recently. One such inhibitor is described in U.S. Patent 5,439,904, *Maiti et al.*

For certain inflammatory diseases having a common pathogenesis, it would be desirable to manipulate current therapy with elastase inhibitor(s), if possible, so as to more specifically, or more effectively, treat the disease(s).

SUMMARY OF THE INVENTION

According to the present invention, a combined therapeutic comprising a suitable antibacterial agent and an elastase inhibitor is used to treat inflammation associated with elastase mediated inflammatory diseases like cystic fibrosis, bronchiectasis, chronic bronchitis, periodontitis and gingivitis. The choice of a suitable antibacterial agent, however, will depend on the nature and level of the disease state. Thus, for cystic fibrosis and bronchiectasis an antibacterial agent effective against *Pseudomonas aeruginosa* and/or *Burkholderia cepacia* will be highly desirable. For chronic bronchitis, an antibacterial agent effective particularly against *Hemophilus influenzae* is desirable. For periodontal disease, an antibacterial agent effective against major oral pathogens involved in gingivitis and/or periodontitis will be a suitable choice.

DETAILED DESCRIPTION OF THE INVENTION

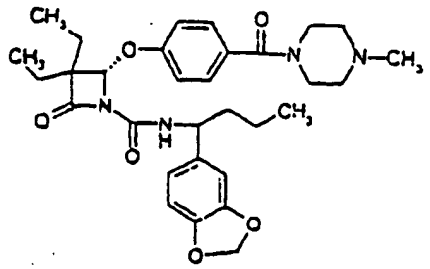
In accordance with the present invention, there is provided a method useful for prevention, control and treatment of inflammatory conditions, particularly of the respiratory system or oral cavity. Suitable pulmonary diseases include, for example, cystic fibrosis (CF), chronic bronchitis, bronchiectasis, and related elastase-mediated disorders. Suitable diseases of the oral cavity include for example, periodontitis and gingivitis. In particular, at least one antibacterial agent is administered in combination with at least one elastase inhibitor to treat such disorders.

It is known that there is a heavy colonization of *Pseudomonas aeruginosa* in the lungs of cystic fibrosis patients in addition to chronic inflammation mediated by elastase. Surprisingly, it now has been discovered that a combination of at least one antipseudomonal antibacterial agent and at least one elastase inhibitor, is an effective therapy for such disease. Indeed, it is shown that a combination of anti-pseudomonal

agent and an elastase inhibitor is more effective as a therapeutic agent in improving lung condition than is an anti-pseudomonal agent or elastase inhibitor alone. Hence, a preferred embodiment of the present invention describes the treatment of elastase mediated disorders, particularly of the lung, such as CF, with a combination of anti-pseudomonal antibacterial agent and elastase inhibitor.

The combination approach preferably useful for treatment of cystic fibrosis, can be used effectively for other inflammatory diseases. Namely, disease states in which aberrant HNE activity is implicated are targets of the combined approach of the invention. For example, chronic bronchitis, bronchiectasis, periodontitis, and related disorders are treated according to the invention.

In a preferred embodiment of the invention, elastase inhibitors useful according to the invention include cephalosporin sulfone derivatives, most preferably, Syn 1390 and Syn 1396, which are described in U.S. Patents 5,439,904, incorporated by reference herein in its entirety. Elastase inhibitors acceptable for the combined therapy include both those of the beta-lactam skeleton, or non-beta lactam skeleton. Several representative elastase inhibitors useful in the context of the present invention include, but are not limited to: SLPI; α_1-AT; DMP 777; ONO 5046; ICI 200,800; ICI 200,355; L-658, 758; L-659, 286; CE-1037; SYN 1390; SYN 1396, whose structures appear below:



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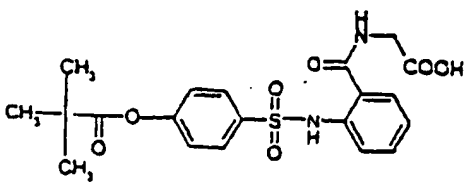

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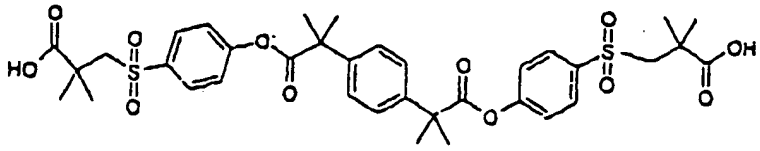

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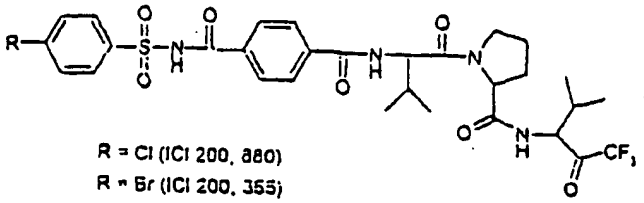

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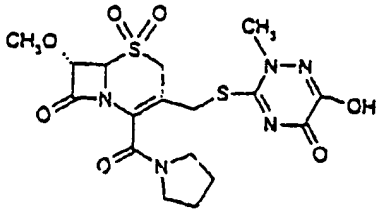
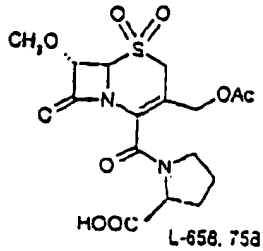
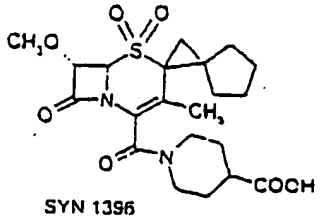


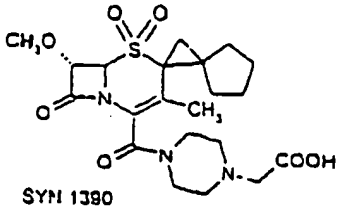
L-659, 286



L-658, 758



SYN 1396



SYN 1390

Additional examples of suitable elastase inhibitors are found in U.S. Patent Nos. 5,446,037; 5,264,430 and 5,258,377, each of which is incorporated by reference herein in its entirety.

Antibacterial agents employed in the present invention include a variety of agents, most preferably, agents directed against *Pseudomonas aeruginosa, Hemophilus influenzae, Burkholderia cepacia*, and major oral pathogens. Examples of antibiotics include agents from the β-lactam class, quinolone class, aminoglycoside class, macrolide class, tetracycline class, cationic peptide class and the like.

Preferred antibacterial agents from the ß-lactam class include, for example, ceftazidime, cefpirome, cefepime, cefoperazone, imipenem, meropenem, piperacillin, mezlocillin, ticarcillin, the combination of piperacillin and tazobactam, the combination of ticarcillin and clavulanic acid, and BMS-180680 (Bristol Myers and Squibb) including their pharmaceutically acceptable salts. Preferred agents from the quinolone class include, for example, norfloxacin, ciprofloxacin, ofloxacin, lomefloxacin, pefloxacin, rufloxacin, and sparfloxacin, including their pharmaceutically acceptable salts. Representative compounds from the aminoglycoside class include, for example, tobramycin, amikacin, gentamicin, and netlimicin, including their pharmaceutically acceptable salts. Representative compounds from the macrolide class include erythromycin, clarithromycin, and azithromycin, including their pharmaceutically acceptable salts. Representative compounds from tetracycline class include tetracycline, oxytetracycline, doxycycline, and minocycline, including their pharmaceutically acceptable salts. Other antibacterial agents included in this invention are: IB-367 (Intrabiotics Pharm, Inc., Mountainview, California, USA), and daptomycin (Cubist Pharmaceuticals, Boston, USA) including their pharmaceutically acceptable salts. For dental disease, a preferred antibacterial agent is triclosan, and related chemical entities used in dental care products, such as, toothpaste, oral rinse, and the like.

Also in accordance with the invention, a kit is provided that is suitable for use in treatment of inflammation associated with elastase-mediated pulmonary disease in a patient in need of such treatment. Such a kit provides at least two separately packaged containers, a first container comprising an effective amount of at least one antibacterial agent according to the present invention, and a second container comprising at least one agent that is an elastase inhibitor in humans. Either of the first or second container, preferably dispenses an aerosol spray. Alternatively, a container according to the

invention may be a vial, blister pack, or other conventional means for holding a pharmaceutically active agent.

DOSAGE

In general, a daily dose of an effective elastase inhibitor or pharmaceutically acceptable salt thereof, of between 1.0 mg and 500 mg per kilogram of body weight, per day, may be administered to a patient, together with the antibacterial agent . The weight ratio of elastase inhibitor to antibiotic with which is administered will normally be in the range of from 1:50 to 50:1, and preferably 1:20 to 20:1. Dose level, however, may vary and depend upon a variety of factors, for example, the activity of the specific compounds employed, the age, body weight, sex, and diet of the patient, and the route of administration.

ROUTE OF ADMINISTRATION

In general, for the pulmonary diseases such as cystic fibrosis, chronic bronchitis, bronchiectasis or other related disorders, the combined therapeutical agent of the present invention will be administered preferably in aerosolized form, such as through a spray or nebulizer. Alternatively, the elastase inhibitor could be administered first followed by the antibiotic or vice versa. Both components of the combined therapy may be delivered by orally or by intravenously as well. For dental diseases, the components of the combined therapy may be delivered in the form of oral rinse, in the form of toothpaste or by injection into the gums locally. For aerosol administration, the combination of elastase inhibitor and antibacterial agent may be formulated as utilizing solutions, suspensions, emulsions, powders and semisolid preparations. For solution formulations, preferred solvents include water, ethanol and glycols. For suspensions, preferred dispersing agents include sorbitad trioleate, oleyl alcohol, oleic acid, lecithin, and the like.

The following example(s) are provided to demonstrate the operability of the present invention.

EXAMPLE I . Efficacy of combined treatment with elastase inhibitor and antibiotic in rat chronic lung infection model.

One hundred eight rats were utilized in these experiments (27 animals in each of four groups). All animals were inoculated intratracheally with 10^5 *Pseudomonas aeruginosa* strain PAO in agar beads. Seven days following inoculation, rats were exposed to aerosol preparations from an Aero-Tech II nebulizer (CIS-US, Bedford, MA). The nebulizer was operated at 45 psi, with a flow rate of 10 L/min, and contained 10 ml of the preparation to be aerosolized. The 10 ml volume was dispensed in 25-30 minutes. Animals were treated daily for seven days: control animals received daily exposure to normal saline; one treatment group received daily exposure to sub-MIC tobramycin ("Tobi"); one treatment group received daily exposure to SYN 1390 (1 mg/ml); one treatment exposure to sub-MIC Tobi plus elastase agent, SYN 1390 (1 mg/ml). Animals were sacrificed on days 0, 3 and 7.

Three animals from treatment and control groups were subjected to bronchoalveolar lavage consisting of 10 ml normal saline at 37°C on days 0, 3 and 7. Lavage fluids were examined, for total cell counts by hemacytometer, neutrophil counts by differential counts (following Wrights staining), and total elastase. Total elastase was measured using the synthetic chromogenic elastin substrate, MeOSAAPVpNA. On days 0, 3 and 7, the left lungs of the three treatment and control animals were removed for quantitative culture, and the left lungs of three treatment and control animals were removed and processed for histopathological examination.

The protocol used included the following steps:

1. Animals were intratracheally inoculated with *Pseudomonas aeruginosa* PSO in beads on Day zero.

2. Animals were randomly divided into 4 treatment groups (27 animals/groups) on day 7, and aerosol treatment was started. Prior to aerosol treatment, all animals were injected with ketamine/atrovet (0.5 dose to induce deep breathing).

3. Animals were treated once per day until sacrifice.

4. Treatments:

Control:	10 ml-2.25 mg/ml NaCl per group of 9 animals
Syn 1390:	10 ml-Syn 1390 1 mg/ml) in 2.15 mg/ml Nail per group of 9 animals.
Tobi:	10 ml Tobi (10mg/ml) in 2.25 mg/ml Nail per group of 9 animals.
Tobi/Syn 1390	10 ml Syn 1390 (1 mg/ml) and Tobi (10 mg/ml) in 2.25 mg/ml Nail per group 9 animals.

5. Nine animals from each group were sacrificed on days 0, 3 and 7 after initiation of aerosol treatment and within 3 hours of the final treatment. Three animals were lavaged and the BAL (broncho alveolar lavage) examined for total cell counts, % PMN and elastase. The lungs from the three animals were quantitatively cultured for *P. aeruginosa* colony forming units. The lungs from three animals were processed for histopathological examination

Table 1. Total cell counts and % PMN in treatment groups.

Treatment Group — Total Cell Counts

	Day 0	Day 3	Day 7
Control	$4.1 \times 10^5 \pm 1.7 \times 10^5$	$3.0 \times 10^5 \pm 4.4 \times 10^4$	$3.1 \times 10^5 \pm 5.0 \times 10^4$
1390	$1.6 \times 10^5 \pm 6.1 \times 10^4$	$2.7 \times 10^5 \pm 4.3 \times 10^4$	$2.4 \times 10^5 \pm 7.7 \times 10^4$
Tobi	$1.8 \times 10^5 \pm 2.0 \times 10^4$	$3.8 \times 10^5 \pm 8.0\ 10^4$	$2.9 \times 10^5 \pm 7.5 \times 10^4$
Tobi/1390	$2.2 \times 10^5 \pm 1.1 \times 10^4$	$1.6 \times 10^6 \pm 1.2\ 10^6$	$3.8 \times 10^5 \pm 4.7 \times 10^4$

Treatment Group — % PMN

	Day 0	Day 3	Day 7
Control	41.7 ± 7.3	4.2 ± 3.4	4.4 ± 2.7
1390	33.1 ± 25	5.3 ± 6.5	1.6 ± 0.4
Tobi	2.5 ± 0.8	1.8 ± 1.1	2.0 ± 2.3
Tobi/1390	5.6 ± 5.4	3.9 ± 2.6	0.3 ± 0.4

Table 2. Quantitative bacteriology in treatment groups.

	Day 0	Day 3	Day 7
Control	$2.5 \times 10^7 \pm 3.4 \times 10^7$	$1.9 \times 10^6 \pm 1.4 \times 10^6$	$1.3 \times 10^7 \pm 2.1 \times 10^7$
1390	$4.5 \times 10^6 \pm 2.5 \times 10^6$	$7.0 \times 10^5 \pm 3.9 \times 10^6$	$3.3 \times 10^5 \pm 3.0 \times 10^5$
Tobi	$1.8 \times 10^5 \pm 1.2 \times 10^4$	$1.3 \times 10^5 \pm 2.1 \times 10^4$	$2.3 \times 10^5 \pm 3.0 \times 10^4$
Tobi/1390	$7.7 \times 10^5 \pm 4.9 \times 10^5$	$5.9 \times 10^4 \pm 1.7 \times 10^4$	$6.1 \times 10^4 \pm 9.4 \times 10^4$

Table 3. Elastase levels in BAL from treatment groups.

Treatment Group Elastase (nM).

	Day 0	Day 3	Day 7
Control	32.3 ± 18.5	21.2 ± 7.4	27.9 ± 8.3
1390	13.9 ± 5.0	18.9 ± 6.4	18.6 ± 1.4
Tobi	18.7 ± 2.8	19.0 ± 9.5	20.2 ± 0.6
Tobi/1390	14.4 ± 4.4	12.6 ± 7.7	12.2 ± 4.0

Table 4. Quantitative pathology on lungs from treatment groups.

Treatment Group % Infiltration (Mean of 3 determinations)

	Day 0	Day 3	Day 7
Control	63	61.5	61
1390	50	38	30
Tobi	32.5	42.3	32
Tobi/1390	42.5	36.7	12.7

Significant observations from the rat data include the values of polymorphonuclear leukocytes (%PMN) at day 7. As shown in Table 1, the PMN releases the destructive enzyme elastase, which degrades the lung tissue, elastin. The reduction of %PMN means the reduction of the level of elastase enzyme. The combination (Tobi/Syn 1) had a value of 0.3 ± 0.4 which was significantly lower than the

individual controls at day 7. In Table 3, the elastase level BAL (broncho alveolar lavage) fluid at day 7 was lower (12.2 ± 4.0) than the controls. This signifies the role of elastase inhibitor. Here"Tobi" stand for aerosol formulation of Tobramycin (the product was obtained from Pathogenesis Corporation of Seattle, USA). Another significant observation was in Table 4, i.e., quantitative pathology on lungs from treatment group at day 7. The value with Tobi/Syn 1390 was 12.7 and the value was significantly lower than each individual control. This data indicates that the combination effectively clears the bacteria *(P. aeruginosa)* from the lung and the conditions of the lungs are improved.

We claim:

1. A method of treating inflammation associated with a human neutrophil elastase mediated disorder, in a patient in need of such treatment, comprising administering an effective amount of at least one antibacterial agent and of at least one agent that is an elastase inhibitor in humans to said patient.

2. A method according to claim 1, wherein said pulmonary disease is selected from the group of pulmonary diseases consisting of cystic fibrosis (CF), chronic bronchitis, and bronchiectasis.

3. A method according to claim 1, wherein said disease is a dental disease selected from the group consisting of periodontitis or gingivitis.

4. A method according to claim 1, wherein said antibacterial agent is selected from the group consisting of ceftazidime, cefpirome, cefepime, cefoperazone, imipenem, meropenem, piperacillin, mezlocillin, ticarcillin, the combination of piperacillin and tazobactam, the combination of ticarcillin and clavulanic acid, BMS-180680, norfloxacin, ciprofloxacin, ofloxacin, lomefloxacin, pefloxacin, rufloxacin, sparfloxacin, tobramycin, amikacin, gentamicin, netlimicin, erythromycin, clarithromycin, azithromycin, tetracycline, oxytetracycline, doxycycline, minocycline, IB-367, daptomycin, triclosan; and pharmaceutically acceptable salts of any of said antibacterial agents.

5. A method according to claim 4, wherein said antibacterial agent is tobramycin, and wherein said elastase inhibitor is SYN 1390 or SYN 1396.

6. A method according to claim 4, wherein said antibacterial agent is IB-367.

7. A method according to claim 4, wherein said antibacterial agent is daptomycin.

8. A method according to claim 1, wherein said elastase inhibitor is selected from the group of elastase inhibitors consisting of DMP 777; ONO 5046; ICI 200,800; ICI 200,355; L-658,758; L-659,286; CE-1037; SYN 1390; SYN 1396; SLPI; and α_1-AT.

9. A method according to claim 1, wherein said elastase inhibitor is administered in an amount of between 1.0 mg and 500 mg per kilogram of body weight, per day, and wherein the weight ratio of elastase inhibitor to antibacterial agent is 1:50 to 50:1.

10. A pharmaceutical composition suitable for treating inflammation associated with an elastase mediated disorder, comprising an effective amount of an elastase inhibitor or pharmaceutically acceptable salt thereof, and an antibacterial agent.

11. A pharmaceutical composition according to claim 10, wherein said elastase inhibitor is selected from the group of elastase inhibitors consisting of DMP 777; ONO 5046; ICI 200,800; ICI 200,355; L-658, 758; L-659, 286; CE-1037; SYN 1390; SYN 1396; SLPI; and α_1-AT.

12. A pharmaceutical composition according to claim 10, wherein said antibacterial agent is selected from the group of antibacterial agents consisting of ceftazidime, cefpirome, cefepime, cefoperazone, imipenem, meropenem, piperacillin, mezlocillin, ticarcillin, the combination of piperacillin and tazobactam, the combination of ticarcillin and clavulanic acid, BMS-180680, norfloxacin, ciprofloxacin, ofloxacin, lomefloxacin, pefloxacin, rufloxacin, sparfloxacin, tobramycin, amikacin, gentamicin, netlimicin, erythromycin, clarithromycin, azithromycin, tetracycline, oxytetracycline, doxycycline, minocycline, IB-367, daptomycin, triclosan; and pharmaceutically acceptable salts of any of said antibacterial agents.

13. A pharmaceutical composition according to claim 10, wherein said composition is provided in aerosol form.

14. A pharmaceutical composition according to claim 13, wherein said aerosol form is a spray.

15. A kit suitable for the treatment in a patient of inflammation associated with an elastase mediated disorder, comprising separately packaged containers, a first container comprising an effective amount of at least one antibacterial agent, and a second container comprising at least one agent that is an elastase inhibitor in humans.

16. A kit according to claim 15, wherein said elastase inhibitor is selected from the group of elastase inhibitors consisting of DMP 777; ONO 5046; ICI 200,800; ICI 200,355; L-658, 758; L-659, 286; CE-1037; SYN 1390; SYN 1396; SLPI; and α_1-AT.

17. A kit according to claim 15, wherein said antibacterial agent is an agent selected from the group consisting of ceftazidime, cefpirome, cefepime, cefoperazone, imipenem, meropenem, piperacillin, mezlocillin, ticarcillin, the combination of

piperacillin and tazobactam, the combination of ticarcillin and clavulanic acid, BMS-180680, norfloxacin, ciprofloxacin, ofloxacin, lomefloxacin, pefloxacin, rufloxacin, sparfloxacin, tobramycin, amikacin, gentamicin, netlimicin, erythromycin, clarithromycin, azithromycin, tetracycline, oxytetracycline, doxycycline, minocycline, IB-367, daptomycin, triclosan; and pharmaceutically acceptable salts of any of said antibacterial agents.

18. A kit according to claim 15, wherein said antibacterial agent is daptomycin.

19. A kit according to claim 15, wherein said antibacterial agent is IB-367.

20. A kit according to claim 15, wherein said antibacterial agent is tobramycin, and wherein said elastase inhibitor is SYN 1390 or SYN 1396.

21. A kit according to claim 15, wherein said elastase mediated disorder is a pulmonary disease selected from the group consisting of cystic fibrosis (CF), chronic bronchitis, and bronchiectasis.

22. A kit according to claim 15, wherein said elastase mediated disorder is a dental disease selected from the group consisting of periodontitis or gingivitis.